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High Asymptomatic Carriage With the Omicron Variant in South Africa

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We report a 23% asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron carriage rate in participants being enrolled into a clinical trial in South Africa, 15-fold higher than in trials before Omicron. We also found lower CD4⁺ T-cell counts in persons with human immunodeficiency virus (HIV) strongly correlated with increased odds of being SARS-CoV-2 polymerase chain reaction (PCR) positive.

Keywords. Omicron variant; asymptomatic carriage; South Africa; SARS-CoV-2; PWH.

The emergence of the B.1.1.529 (Omicron) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, first identified in Botswana and South Africa [1] and now detected in over 165 countries, has led to a new global wave of coronavirus disease 2019 (COVID-19). In mid-November 2021, South Africa experienced a new rise in COVID-19 cases at a rate faster than any of the 3 previous waves [2], even in settings of ongoing mask mandates and high prevalence of prior infection [3, 4]. The early widespread dissemination of Omicron globally indicated a need to better understand the transmission dynamics of Omicron, including asymptomatic spread among immunocompetent and immunocompromised populations.

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METHODS

On 2 December 2021, we began enrolling participants into the Ubuntu multicenter Phase 3 clinical trial in sub-Saharan Africa (with all sites initially enrolling located in South Africa) to assess the relative risk of the COVID-19 mRNA vaccine mRNA-1273 between study groups in persons (adults) with human immunodeficiency virus (HIV, PWH) or another comorbidity known to be associated with severe COVID-19 (CoVPN 3008, NCT05168813). A smaller number of HIV negative persons was also included. Previously vaccinated individuals were excluded. Baseline testing included HIV screening, CD4⁺ T-cell count and HIV viral load (if HIV positive), and collection of a nasal swab for SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) testing with the Abbott Real-Time SARS-CoV-2 assay (Abbott Laboratories, Abbott Park, IL, USA). The Assure Ecotest IgG/IgM Rapid Test (Assure Tech, Hangzhou, China) was used to determine baseline SARS-CoV-2 antibody status at screening. TaqPath™ COVID 19 CE IVD RT PCR (ThermoFisher, Waltham, Massachusetts, USA) was used to amplify Orf and N genes. Study participants had to be clinically well with no signs/symptoms of COVID-19 to be vaccinated upon enrollment. Results from the Ubuntu trial were compared with results of participants in the Sisonke sub-study and Ensemble 1 trials.

The Ubuntu, Sisonke, and Ensemble 1 trials were approved by the South African Health Products Regulatory Authority (SAHPRA) and by all local South African research ethics committees. Patient/participant consent was obtained, and the appropriate institutional forms have been archived.

RESULTS

As of 20 January 2022, a total of 1172 adults were enrolled in the Ubuntu trial across eight South African provinces (see [Supplementary Methods](#) for list of clinical research sites). The median age of participants was 40 years (range 18–76 years), and 76% were assigned female sex at birth.

Baseline nasal swab data were available for 719/1172 (61.3%) enrolled participants: 162 (23%) of whom had asymptomatic SARS-CoV-2 infection by RT-PCR ([Supplementary Table 1](#)). Province-wide prevalence data can be found in [Supplementary Table 2](#). SARS-CoV-2 infection was more frequent among SARS-CoV-2 seronegative (95/317) compared to seropositive (67/402) participants, regardless of baseline HIV status (30% vs 17%, $P < .001$) ([Supplementary Table 2](#)). SARS-CoV-2 infection was detected among 51/153 (33%) of PWH with a CD4⁺ T-cell count <500 cells/mm³ vs 66/354 (19%) of PWH with counts ≥ 500 cells/mm³ ($P < .001$) ([Figure 1A](#)), an association seen in both SARS-CoV-2 seropositive and seronegative

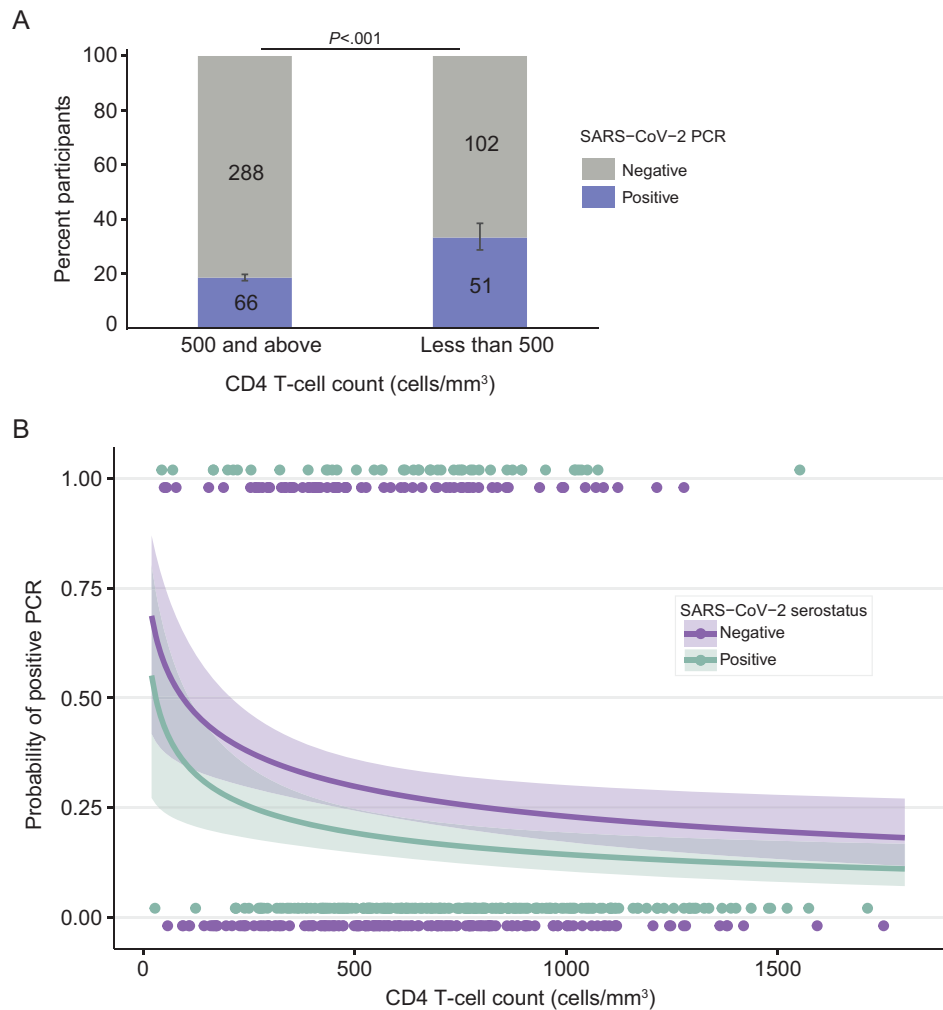


Figure 1. A, Percent of PWH positive for SARS-CoV-2 PCR (blue) among those with CD4⁺ T-cell counts ≥ 500 and < 500 cells/mm³. Error bars show 95% CI. Actual numbers of individuals in each group are displayed on the bar graphs. B, Probability of PCR positivity by CD4⁺ T-cell count among PWH. Dots display observed data in baseline seronegative (purple) and seropositive (green) asymptomatic study participants. Positive and negative PCR results are plotted around 1 and 0 with a small vertical offset by serostatus for clarity. Lines and shaded regions display the estimated probability of positive PCR and corresponding 95% CIs, respectively. Logistic regression was used to model the probability of PCR positivity by CD4 count, adjusting for baseline serostatus. Abbreviations: CI, confidence interval; PCR, polymerase chain reaction; PWH, people with human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

PWH (Supplementary Table 3). A 10-fold decrease in CD4 count corresponded to a 3.2-fold higher odds of a positive PCR test, after adjusting for serostatus (95% confidence interval [CI]: 1.16–3.03 fold higher, $P = .003$, Figure 1B). Although all SARS-CoV-2 cases were identified during the Omicron outbreak, 62 of the initial 72 infections underwent additional testing to evaluate S gene dropout, and the Orf and N genes were successfully amplified for 56 of these samples. All 56 had S gene dropout, suggestive of Omicron infection [5]. Sequencing was successful for 38 of these 56 samples, and all were confirmed as Omicron. The median RT-PCR cycle threshold (Ct) value was 25.8 (range 14.4–34.9), with Ct values < 25 in 27/56 (48%) and ≤ 20 in 10/56 (18%) of participants (Supplementary Figure 1; Supplementary Table 4).

Symptom data were available for 87/162 SARS-CoV-2 positive participants for the 7-day period following the positive PCR result: 52/87 (60%) remained without symptoms, of whom 18 were seropositive and 34 seronegative (Supplementary Table 5).

Nasal swab sampling at the initial vaccination visit has been used in several COVID-19 vaccine efficacy trials to define persons infected at the time of study entry [6–9]. Studies conducted before Omicron consistently exhibited asymptomatic carriage of pre-Omicron variants in $< 2\%$ of participants at such visits [6, 7, 9] (Supplementary Table 1), including a 1227 PWH subgroup in the Ensemble 1 study [7], largely enrolled during the Beta outbreak in South Africa. In addition to these studies, the Sisonke study [8], conducted exclusively in South Africa between June and August 2021 during the Beta

and Delta outbreaks, demonstrated an asymptomatic carriage rate of 2.4% in the subgroup sampled on day of vaccination. Of the 577 participants of the Sisonke subgroup resampled from mid-November to 7 December 2021, at the 6-month follow-up visit (time of Omicron outbreak), 91/577 (16%) participants had SARS-CoV-2 detected in their nasal swab sample despite prior vaccination (Supplementary Table 6). In this cohort, the frequency of PCR positivity with Omicron was similar between PWH (27/169: 16%) and HIV negative participants (62/405: 15.3%).

DISCUSSION

The prevalence of asymptomatic infection seen in our study (23%) strongly suggests that Omicron has a much higher rate of asymptomatic carriage than other variants of concern (VoC). Studies prior to Omicron have shown that 30-40% of SARS-CoV-2 infections are asymptomatic [10, 11]. Our data suggest that a much higher proportion of Omicron infections may be asymptomatic; data consistent with the pattern of milder disease seen with Omicron in general. Importantly, many of these asymptomatic carriers identified in our study and others had high nasal viral titers, as indicated by the relatively low RT-PCR Ct values [12]. The high prevalence of cryptic carriage of Omicron helps explain its widespread dissemination globally, presenting a substantial challenge to many current infection control strategies, including symptom-triggered testing, contact tracing, and masking policies.

Our findings that large numbers of PWH could be at elevated risk of shedding Omicron and that lower CD4⁺ T-cell counts may be associated with an increased likelihood of being PCR positive for SARS-CoV-2 are both provocative and perhaps conceptually obvious. The data are provocative because the cutoff point was seen at the relatively high level of <500 cells/mm³, although more data are needed to validate this finding. Prior studies largely conducted during ancestral strain time periods have not found an increased prevalence of SARS-CoV-2 among PWH compared to HIV-uninfected people [13–16]. VoC that exhibit levels of resistance to the immunodominant epitopes associated with immune protection may be a factor in these differences [17]. Our findings do not differentiate whether PWH with CD4 counts <500 cells/mm³ have a greater risk of acquiring SARS-CoV-2, or whether their high subclinical prevalence of Omicron infection is related to impaired clearance of the virus. Persistent viral replication is of significant public health importance both in terms of transmission risk as well as the risk of viral evolution and generation of further VoC. Studies of viral persistence and viral variation among PWH are needed. Persistent SARS-CoV-2 viral shedding may not simply be limited to individuals off treatment and with the most advanced HIV disease but could also impact many PWH on antiretroviral therapy (ART) with more controlled disease.

Study limitations include unclear generalizability outside of South Africa, particularly to places with lower SARS-CoV-2 seroprevalence. Furthermore, the interpretation of positive SARS-CoV-2 serology tests was limited by the fact that they could not differentiate between which strains led to the antibodies (eg, Delta, Omicron) or when the infections took place—including potentially ongoing infections.

The widespread asymptomatic carriage found with Omicron indicates that investment in second-generation vaccines to prevent infection, not only disease, and enhanced surveillance with rapid testing paired with real-time whole genome sequencing should be explored. These data also highlight the urgent need for larger studies to better characterize how immunocompromise influences infection acquisition and clearance. The rapid dissemination of Omicron related to this high rate of subclinical infection has highlighted our interconnectedness, and research that helps us protect at-risk populations will also serve to protect us all.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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